Original Investigation

Myocardial Infarction and Ischemic Heart Disease in Overweight and Obesity With and Without Metabolic Syndrome

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IMPORTANCE Overweight and obesity likely cause myocardial infarction (MI) and ischemic heart disease (IHD); however, whether coexisting metabolic syndrome is a necessary condition is unknown.

OBJECTIVE To test the hypothesis that overweight and obesity with and without metabolic syndrome are associated with increased risk of MI and IHD.

DESIGN, SETTING, AND PARTICIPANTS We examined 71 527 individuals from the Copenhagen General Population Study and categorized them according to body mass index (BMI) as normal weight, overweight, or obese and according to absence or presence of metabolic syndrome.

MAIN OUTCOMES AND MEASURES Hazard ratios for incident MI and IHD according to combinations of BMI category and absence or presence of metabolic syndrome.

RESULTS During a median of 3.6 years' follow-up, we recorded 634 incident MI and 1781 incident IHD events. For MI, multivariable adjusted hazard ratios vs normal weight individuals without metabolic syndrome were 1.26 (95% CI, 1.00-1.61) in overweight and 1.88 (95% CI, 1.34-2.63) in obese individuals without metabolic syndrome and 1.39 (95% CI, 0.96-2.02) in normal weight, 1.70 (95% CI, 1.35-2.15) in overweight, and 2.33 (95% CI, 1.81-3.00) in obese individuals with metabolic syndrome. For IHD, results were similar but attenuated. Normal weight vs overweight vs obesity and presence vs absence of metabolic syndrome did not interact on risk of MI or IHD ($P = .90$ and $P = .44$). Among individuals both with and without metabolic syndrome there were increasing cumulative incidences of MI and IHD from normal weight through overweight to obese individuals (log-rank trend $P = .006$ to $P < .001$). Although the multivariable adjusted hazard ratio for MI in individuals with vs without metabolic syndrome was 1.54 (95% CI, 1.32-1.81) across all BMI categories, addition of metabolic syndrome to a multivariable model including BMI and other clinical characteristics improved the Harell C-statistic only slightly for risk of MI (comparison $P = .03$) but not for IHD ($P = .41$).

CONCLUSIONS AND RELEVANCE These findings suggest that overweight and obesity are risk factors for MI and IHD regardless of the presence or absence of metabolic syndrome and that metabolic syndrome is no more valuable than BMI in identifying individuals at risk.

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The association between overweight or obesity and ischemic heart disease is well established in observational studies,[1,2] and using a mendelian randomization approach, we recently added evidence to support that this relationship is causal.[3] One plausible mechanism for this link is that overweight and obesity often are accompanied by metabolic syndrome, a cluster of cardiovascular risk factors consisting of hypertension, dyslipidemia, and hyperglycemia.[4] Over the years, there has been considerable disagreement over the diagnostic criteria of metabolic syndrome.[4] Despite this, it is widely accepted that metabolic syndrome per se is associated with an increased risk of ischemic cardiovascular events.[5-7] However, among overweight and obese individuals, some will, despite excessive body fat, have no or only a few other cardiovascular risk factors.[8,9] Whether coexisting metabolic syndrome is a necessary condition for the development of ischemic cardiovascular disease in overweight and obese individuals remains controversial.[10-12] Indeed, abdominal obesity is a central and previously obligatory component of metabolic syndrome that may be sufficient to identify individuals at increased risk of future cardiovascular events, even in the absence of other metabolic abnormalities. If this is the case, the overall clinical utility of metabolic syndrome in overweight and obese individuals could be questioned.

In the present study, we tested the hypothesis that overweight and obesity with and without metabolic syndrome is associated with increased risk of myocardial infarction and ischemic heart disease. For this purpose, we examined 71 527 individuals from the Copenhagen General Population Study and categorized them according to their body mass index (BMI) as normal weight, overweight, or obese and according to absence or presence of metabolic syndrome. During a median of 3.6 years' follow-up, we recorded hospital admissions and deaths due to myocardial infarction and ischemic heart disease.

Methods

Participants

We studied individuals from the Copenhagen General Population Study,[13-15] an ongoing prospective population study initiated in 2003. Individuals were randomly selected on the basis of the national Danish Civil Registration System to reflect the population aged 20 to 100 years. All participants were whites of Danish descent, defined according to the Danish Civil Registration System and requiring that the participant and both parents be Danish citizens born in Denmark. The participation rate was 45%. Examinations included a questionnaire, physical measurements, and blood sampling. The study was conducted according to the Declaration of Helsinki and approved by Herlev Hospital and a Danish institutional review board. Written informed consent was obtained from all participants.

Between 2003 and 2011, 77 270 individuals had been examined and had complete information on BMI, waist measurement, blood pressure, and biochemical analyses enabling determination of their BMI category and the absence or presence of metabolic syndrome; 351 individuals with missing information were excluded. After also excluding 661 individuals with a BMI (calculated as weight in kilograms divided by height in meters squared) less than 18.5 and 5082 individuals with a diagnosis of ischemic heart disease prior to study entry, we had 71 527 individuals available for analyses.

Baseline Examinations

Body mass index was calculated as measured weight in kilograms divided by measured height in meters squared. Waist circumference was measured at the midpoint between the lower end of the rib cage and the upper part of the pelvic bone. Standard systolic and diastolic blood pressure was measured once using an automatic Digital Blood Pressure Monitor (Kivex). Using nonfasting plasma samples, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, and C-reactive protein levels were measured using standard hospital assays. Information on antihypertensive medication, antidiabetic treatment, aspirin use, and lipid-lowering therapy was self-reported. Because we did not have information on medication specifically aimed at lowering triglyceride levels otherwise used in the diagnostic criteria of metabolic syndrome,[4] we corrected nonfasting triglyceride levels for use of any lipid-lowering therapy. To do so, information on the type of lipid-lowering agents received by 13 466 participants was retrieved from the Danish Registry of Medicinal Product Statistics. These participants had received at least 1 prescription of a lipid-lowering agent during the study period from 2003 to 2011. Because these data showed that most individuals (approximately 83%) were using simvastatin (eTable 1 in Supplement) and assuming a typical dose of 40 mg daily, nonfasting triglyceride levels were multiplied by 1.11 in individuals receiving lipid-lowering medication, corresponding to an estimated 10% reduction in triglycerides, prior to the diagnostic classification.[16] Smokers were defined as current smokers, and physical inactivity was defined as leisure time activity less than 4 hours weekly and predominantly sedentary work.

Overweight and Obesity

Individuals were categorized as normal weight with a BMI of 18.5 to 24.9, overweight with BMI of 25.0 to 29.9, and obese with a BMI at least 30.0. Although categorization may lead to loss of information compared with using BMI as a continuous variable, we used these cut points because they are simple and clinically useful.

Metabolic Syndrome

We used a slightly modified version of the harmonized metabolic syndrome definition[4] because all components included are easily measured in clinical practice. Metabolic syndrome was defined as 3 or more of the following 5 metabolic abnormalities: (1) waist circumference at least 94 cm in men and at least 80 cm in women, (2) systolic blood pressure at least 130 mm Hg and/or diastolic blood pressure at least 85 mm Hg and/or antihypertensive treatment, (3) nonfasting plasma triglyceride level at least 150 mg/dL (to convert to millimoles per liter, multiply by 0.0113), (4) high-density lipoprotein cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in

women (to convert to millimoles per liter, multiply by 0.0259), and (5) registry-documented diagnosis of diabetes mellitus and/or self-reported diabetes mellitus and/or antidiabetic treatment and/or nonfasting plasma glucose level more than 200 mg/dL (to convert to millimoles per liter, multiply by 0.0555).

End Points

Information on diagnosis of myocardial infarction and ischemic heart disease (World Health Organization *International Classification of Diseases, Eighth Revision*, codes 410-414 and 410; *International Classification of Diseases, Tenth Revision,* codes I20-I25 and I21-I22) was collected from 2003 until 2011 by reviewing all hospital admissions and diagnoses entered in the national Danish Patient Registry and all causes of death entered in the national Danish Causes of Death Registry.[3,14,15] A diagnosis of myocardial infarction was based on characteristic chest pain, electrocardiographic changes, and/or elevated cardiac enzyme levels. The ischemic heart disease diagnosis was broader and included angina pectoris, revascularization procedures, and/or myocardial infarction.

Statistical Analyses

We used Stata/SE, version 12.0 (StataCorp). In prospective analyses, we estimated hazard ratios (HRs) and cumulative incidence curves for myocardial infarction and ischemic heart disease as a function of age by means of Cox regression analysis. A log-rank test was used to compare incidence curves; for trend tests, normal weight, overweight, and obesity were coded 1, 2, and 3. Models were adjusted for age (as timescale), sex, smoking, plasma low-density lipoprotein cholesterol level, lipid-lowering medication use (approximately 97% of participants receiving such medications were prescribed statins) (eTable 1 in Supplement), aspirin use, and physical inactivity. Because hypertension, elevated plasma triglyceride levels, low high-density lipoprotein cholesterol level, hyperglycemia, diabetes mellitus, and waist circumference are all part of the definition of metabolic syndrome (as stratified for) and/or part of the biological pathway from overweight and obesity to myocardial infarction and ischemic heart disease, we decided a priori not to adjust for these covariates. The proportional hazard assumption was judged by visual inspection of cumulative hazard logarithm plots against age; no major violations were observed. A test of interaction in the Cox model was performed by introducing a 2-factor interaction term, and *P* values were calculated by likelihood ratio test for comparing models with and without interaction terms. In analyzing age interaction, follow-up was the underlying timescale. The added discriminative power offered by the addition of metabolic syndrome to a basic model including BMI and clinical characteristics was analyzed using the Harrell C-index.[17] In mediation analyses, percentage of excess risk mediated was calculated as $[(HR_{con\ adj} - HR_{con\ +\ med\ adj})/(HR_{con\ adj} - 1)] \times 100\%$, where $HR_{con\ adj}$ is the confounder-adjusted HR for myocardial infarction or ischemic heart disease and $HR_{con\ +\ med\ adj}$ is the confounder and mediator-adjusted HR.[18] Follow-up time for each participant began at study entry and ended at event, death (n = 1759), emigration (n = 238), or May 2011, whichever came first. Because we only included individuals from the cohort with complete information on BMI, all components of metabolic syndrome, and covariates for adjustments, we had no individuals with missing values.

Results

Baseline characteristics of the 71 527 individuals included in the study are seen stratified by BMI category (normal weight, overweight, obese) and by the absence or presence of metabolic syndrome (**Table**) and stratified by event status (eTable 2 in Supplement). Among these, 31 452 individuals (44%) were normal weight, 28 579 overweight (40%), and 11 496 individuals (16%) were obese. Numbers of individual metabolic syndrome components present in normal weight, overweight, and obese individuals are seen in eTable 3 in the Supplement. Metabolic syndrome was present in 10% of normal weight, in 40% of overweight, and in 62% of obese individuals. Among individuals with metabolic syndrome, BMI was higher within each BMI category compared with those without metabolic syndrome (**Figure 1**).

Characteristics stratified by sex are shown in eTables 4, 5, and 6 in the Supplement. Among the 31 357 male participants, 10 522 were normal weight (34%), 15 550 were overweight (50%), and 5285 individuals (17%) were obese. Corresponding numbers among the 40 170 female participants were 20 930 (52%), 13 029 (32%), and 6211 (15%), respectively.

Myocardial Infarction and Ischemic Heart Disease

During a median (interquartile range) follow-up time of 3.6 (2.4-5.7) years, 634 individuals received a diagnosis of myocardial infarction, and 1781 individuals, a diagnosis of ischemic heart disease. As expected, the cumulative incidences of myocardial infarction and ischemic heart disease were higher in overweight and obese vs normal weight individuals (both log-rank trend $P < .001$) (**Figure 2**A and Figure 2B). Multivariable adjusted HRs for myocardial infarction vs normal weight individuals were 1.38 (95% CI, 1.14-1.67) in overweight and 2.04 (95% CI, 1.64-2.54) in obese individuals. Corresponding HRs for ischemic heart disease were 1.25 (95% CI, 1.12-1.40) and 1.64 (95% CI, 1.44-1.86). Also, the presence of metabolic syndrome was associated with increased cumulative incidences of myocardial infarction and ischemic heart disease (both log-rank $P < .001$) (Figure 2C and Figure 2D). Multivariable adjusted HRs for myocardial infarction and ischemic heart disease in individuals with vs without metabolic syndrome were 1.54 (95% CI, 1.32-1.81) and 1.38 (95% CI, 1.26-1.52). Including adjustment for BMI as a continuous variable, risk estimates were almost identical. Risk of myocardial infarction and ischemic heart disease increased stepwise according to the presence of 1, 2, 3, 4, or 5 components of metabolic syndrome (eFigure 1 in Supplement). Hazard ratios with 95% confidence intervals for each of the components of metabolic syndrome and other cardiovascular risk factors individually are shown in eTable 7 in the Supplement.

When individuals were divided into groups according to their BMI category (normal weight, overweight, obesity) and absence or presence of metabolic syndrome, risk of myocar-

Table. Baseline Characteristics of Participants According to Body Mass Index Categories and Presence or Absence of Metabolic Syndrome

Characteristic	Without Metabolic Syndrome			With Metabolic Syndrome		
	Normal Weight[a]	Overweight[a]	Obese[a]	Normal Weight[a]	Overweight[a]	Obese[a]
Patients, No.	28 431	17 406	4416	3021	11 173	7080
Age, median (IQR), y	53 (44-63)	56 (47-65)	58 (48-67)	60 (51-70)	60 (51-68)	58 (49-66)
Men, %	33	49	32	38	62	55
Whites of Danish descent, %	100	100	100	100	100	100
BMI, median (IQR)	23 (21-24)	27 (26-28)	32 (31-34)	24 (23-25)	28 (26-29)	33 (31-35)
Waist circumference, median (IQR), cm	79 (74-85)	91 (85-96)	103 (96-110)	87 (82-94)	97 (92-102)	108 (101-114)
Blood pressure, median (IQR), mm Hg						
Systolic	132 (120-147)	138 (125-153)	144 (130-160)	143 (132-156)	146 (135-160)	150 (137-162)
Diastolic	80 (73-87)	83 (76-90)	86 (80-94)	85 (79-90)	87 (80-94)	89 (82-96)
Medication use, %						
Antihypertensive	9	13	19	22	24	31
Aspirin	6	8	9	13	12	14
Lipid-lowering	4	6	6	11	12	14
Plasma levels, median (IQR)						
Total cholesterol, mg/dL	212 (185-232)	216 (193-239)	220 (197-236)	224 (197-255)	224 (201-255)	224 (201-251)
Low-density lipoprotein cholesterol, mg/dL	120 (100-139)	127 (108-147)	127 (112-151)	127 (108-154)	131 (112-158)	131 (108-158)
High-density lipoprotein cholesterol, mg/dL	69 (58-81)	62 (54-73)	66 (54-69)	50 (42-66)	50 (39-58)	46 (39-54)
Triglycerides, mg/dL	106 (71-133)	115 (89-142)	124 (97-133)	195 (168-248)	204 (168-265)	212 (177-283)
Glucose, mg/dL	92 (85-99)	92 (85-99)	94 (86-99)	96 (86-105)	96 (88-105)	97 (88-108)
C-reactive protein, mg/L	1.3 (0.9-1.7)	1.5 (1.1-2.2)	2.2 (1.5-4.2)	1.6 (1.1-2.6)	1.7 (1.3-2.9)	2.5 (1.6-4.4)
Diabetes mellitus, %	1	0	0	8	7	11
Current smokers, %	18	15	13	29	20	19
Physical inactivity,[b] %	34	35	44	45	45	49

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

SI conversion factors: To convert total cholesterol, low-density lipoprotein cholesterol, or high-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert glucose to millimoles per liter, multiply by 0.0555; to convert C-reactive protein to nanomoles per liter, multiply by 9.524.

[a] Normal weight, 18.5 to 24.9; overweight, 25.0 to 29.9; obese, 30.0 or higher.

[b] Defined as leisure time activity less than 4 hours weekly and predominantly sedentary work.

dial infarction and ischemic heart disease increased with higher BMI category independent of presence or absence of metabolic syndrome (**Figure 3**A). For myocardial infarction, multivariable adjusted HRs vs normal weight individuals without metabolic syndrome were 1.26 (95% CI, 1.00-1.61) in overweight and 1.88 (95% CI, 1.34-2.63) in obese individuals without metabolic syndrome and 1.39 (95% CI, 0.96-2.02) in normal weight, 1.70 (1.35-2.15) in overweight, and 2.33 (95% CI, 1.81-3.00) in obese individuals with metabolic syndrome. For ischemic heart disease, corresponding HRs were 1.08 (95% CI, 0.95-1.24), 1.45 (95% CI, 1.20-1.77), 1.03 (95% CI, 0.82-1.30), 1.30 (95% CI, 1.13-1.49), and 1.67 (95% CI, 1.44-1.93), respectively. There were no interactions between BMI and absence or presence of metabolic syndrome on risk of myocardial infarction and ischemic heart disease when BMI was categorized (normal weight, overweight, obese) (P = .90 and P = .44) or used continuously (P = .91 and P = .79). Stratifying for sex gave slightly higher risk estimates for myocardial infarction in women but attenuated results in men (Figure 3B). For ischemic heart disease, risk estimates were higher in men but attenuated in women.

Among individuals without metabolic syndrome, there were increasing cumulative incidences of myocardial infarction from normal weight through overweight to obese individuals (log-rank trend P = .001) (eFigure 2, upper left panel, in Supplement); this was also the case for cumulative incidences of ischemic heart disease (log-rank trend P < .001) (eFigure 2, upper right panel, in Supplement). Among individuals with metabolic syndrome, there likewise were increasing cumulative incidences of myocardial infarction and ischemic heart disease from normal weight through overweight to obese individuals (log-rank trend P = .006 and P < .001) (eFigure 2, lower panels, in Supplement). Stratifying for BMI category, presence vs absence of metabolic syndrome within overweight and obese individuals was associated with slightly increased cumulative incidences of myocardial infarction and ischemic heart disease (log-rank P = .03 to P < .001) (eFigure 3 in Supplement).

Prediction and Mediation

The addition of metabolic syndrome to a model including BMI (as a continuous variable), age, sex, smoking, plasma low-

density lipoprotein cholesterol level, lipid-lowering medication use (statins for approximately 97% of participants receiving such medication), aspirin use, and physical inactivity improved the Harell C-statistic only slightly for risk of myocardial infarction (0.71 to 0.72; comparison $P = .03$) but not for ischemic heart disease (0.60 for both models; comparison $P = .41$). Also, the percentage of excess risk mediated by metabolic syndrome in the association between BMI (as a continuous variable) and both end points was 12%; that is, 12% of the associated effect size of BMI on risk of myocardial infarction and ischemic heart disease is explained by metabolic syndrome. When BMI was categorized (normal weight, overweight, obese), this proportion increased to 23% for myocardial infarction and 16% for ischemic heart disease. These estimates and the results of other mediation analyses with BMI as the mediator and metabolic syndrome as exposure are shown in eTable 8 in the Supplement.

Sensitivity Analyses

In sensitivity analyses, we first defined metabolic syndrome as the presence of 2 or more metabolic abnormalities. Using this definition, the most common metabolic abnormality among overweight and obese individuals without metabolic syndrome was increased waist circumference (78% of overweight and 99% of obese individuals) (eTable 9 in Supplement), and risks were similar for obese but attenuated for overweight individuals without metabolic syndrome (eFigure 4 in Supplement). Furthermore, excluding waist circumference as a diagnostic criterion and defining the presence of metabolic syndrome as the presence of 2 or more abnormalities gave similar results (eFigure 5 in Supplement). Also, additional adjustment for waist circumference, antihypertensive medication use, and systolic and diastolic blood pressure, categorizing all participants receiving lipid-lowering therapy as having high triglyceride levels regardless of the measured value, changing the nonfasting serum glucose threshold from more than 200 mg/dL to at least 100 mg/dL for defining hyperglycemia, or exclusion of individuals with diabetes mellitus at baseline (n = 2063) gave similar results to those presented in Figure 3 (eFigures 6-9 in Supplement). Finally, using the composite end point of myocardial infarction, ischemic heart disease, and all-cause mortality, risk estimates were largely similar to those presented in Figure 3A (eFigure 10 in Supplement).

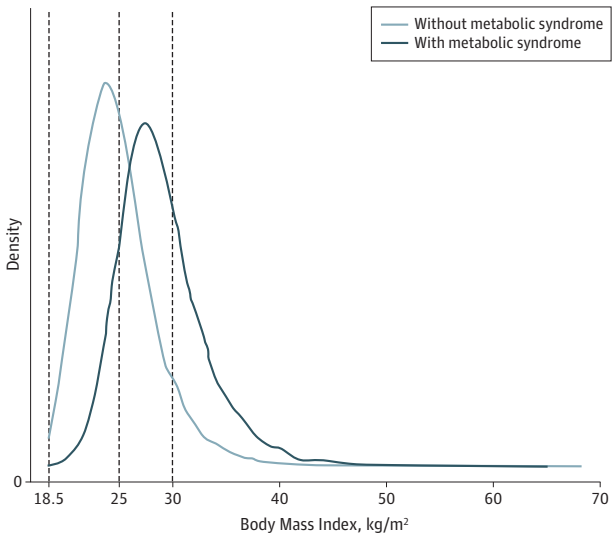
Discussion

In the present study, we examined 71 527 individuals from the Copenhagen General Population Study and found that overweight and obesity were associated with increased risk of myocardial infarction and ischemic heart disease independent of the presence or absence of metabolic syndrome.

Using a mendelian randomization approach, we have recently added evidence to support a causal link between increased BMI and increased risk of ischemic heart disease.[3] The suggested mechanism for this link is through obesity-related risk factors such as hypertension, dyslipidemia, and hyperglycemia, all components of metabolic syndrome.[4] Indeed, our findings in the present study may be explained by overweight and obese individuals without metabolic syndrome at baseline developing the other components of the syndrome over time, which later leads to a cardiovascular event. In support of this hypothesis, abdominal obesity often precedes the other components[19-23] and may even be causal in the development of other cardiovascular risk factors such as hypertension.[24] Furthermore, BMI was relatively higher within each BMI category in individuals with metabolic syndrome, and this may explain some of the excess risk observed in these individuals compared with those without metabolic syndrome. Also, the addition of metabolic syndrome only slightly increased the capacity of BMI and other clinical characteristics to predict myocardial infarction and no increment was observed in predicting ischemic heart disease. This was also supported by mediation analyses, which suggested that only a minor proportion of the increased risk observed for BMI is explained by metabolic syndrome. Thus, our findings suggest that metabolic syndrome is no more valuable than BMI in identifying individuals at risk of ischemic cardiovascular disease and may call into question the overall clinical utility of metabolic syndrome in overweight and obese individuals.

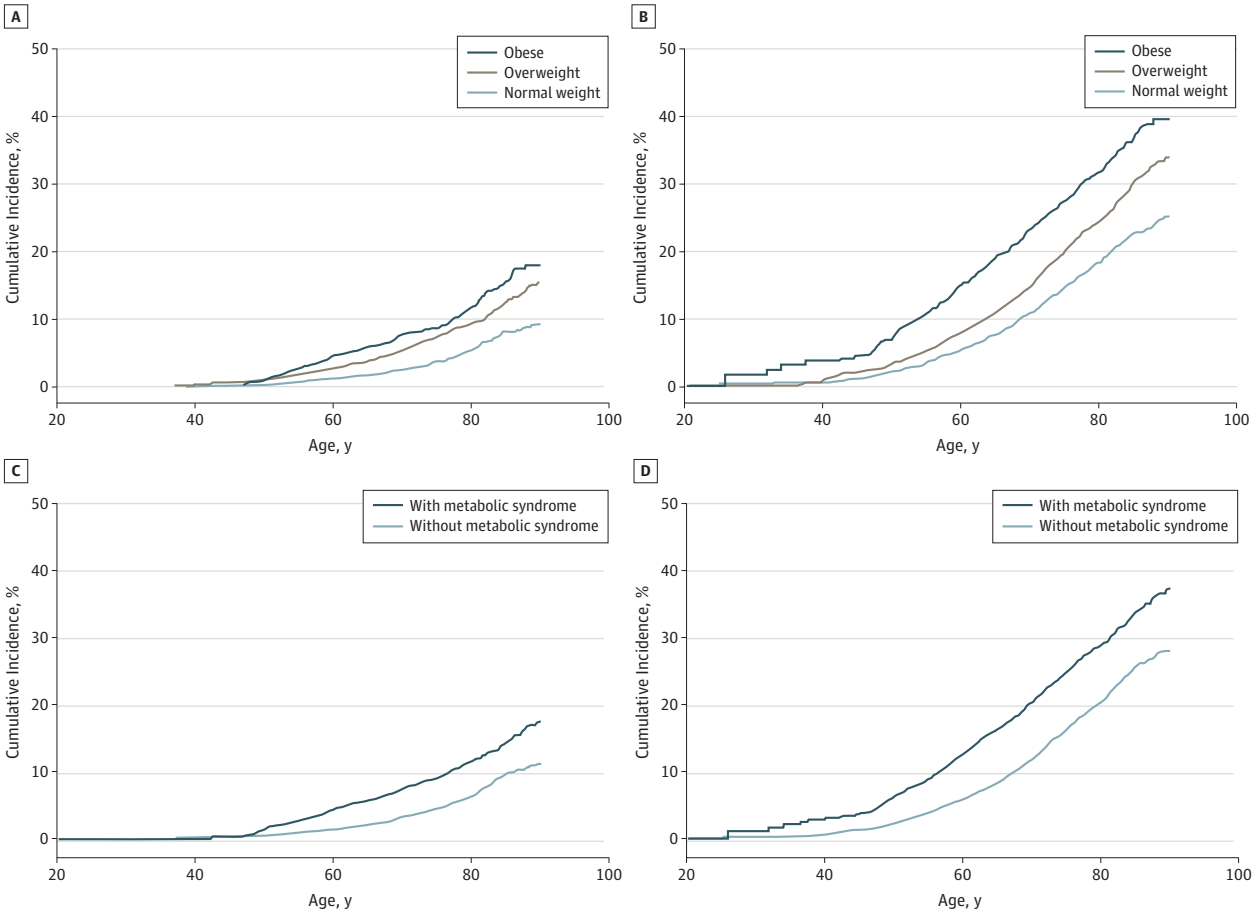
Previous studies using an approach similar to that of the present study have had conflicting results.[10-12,25] Some studies have found no increased risk of cardiovascular disease in overweight and obese individuals without metabolic syndrome, leading to suggestions that overweight and obesity in these individuals are benign conditions.[11,12,25] In contrast, 1 study of middle-aged Swedish men with more than 30 years of follow-up found an increased risk of cardiovascular disease in overweight and obese individuals without metabolic

Figure 1. Distribution of Body Mass Index (BMI) According to the Absence or Presence of Metabolic Syndrome



Data are based on 71 527 individuals from the Copenhagen General Population Study without prior diagnoses of ischemic heart disease. Dashed lines indicate divisions between the categories of BMI (calculated as weight in kilograms divided by height in meters squared) (normal weight, 18.5-24.9; overweight, 25.0-29.9; obese, ≥30.0).

Figure 2. Cumulative Incidences of (Left) Myocardial Infarction (MI) and (Right) Ischemic Heart Disease (IHD) as a Function of Age According to Body Mass Index (BMI) Category (Normal Weight, Overweight, Obese) and Absence or Presence of Metabolic Syndrome



A, The hazard ratios (HRs) for MI vs normal weight individuals were 1.38 (95% CI, 1.14-1.67) in overweight and 2.04 (95% CI, 1.64-2.54) in obese individuals (log-rank trend $P < .001$). B, The HRs for IHD vs normal weight individuals were 1.25 (95% CI, 1.12-1.40) and 1.64 (95% CI, 1.44-1.86). C, The HR for MI in individuals with vs without metabolic syndrome was 1.54 (95% CI, 1.32-1.81). D, The HR for IHD in individuals with vs without metabolic syndrome was 1.38 (95% CI, 1.26-1.52). Data are based on 71 527 individuals from the Copenhagen General Population Study without prior diagnoses of IHD. Hazard ratios were adjusted for age, sex, smoking, plasma low-density lipoprotein cholesterol level, lipid-lowering medication use (statins for approximately 97% of participants receiving such medication), aspirin use, and physical inactivity. Body mass index was calculated as weight in kilograms divided by height in meters squared.

syndrome vs normal weight individuals without metabolic syndrome.[10] The inconsistencies between these former studies may be caused by differences in defining metabolic syndrome and/or the cohort selection criteria. Also, studies with small sample sizes or a low number of events may not have enough statistical power to discriminate differences in risk for the relatively small fraction of overweight and obese individuals without metabolic syndrome. To our knowledge, the present study is the largest to date including both men and women in different age groups using a slightly modified version of a simple and widely accepted harmonized definition of metabolic syndrome.[4] Our findings suggest that overweight and obesity even in the absence of metabolic syndrome are not benign conditions.

Some limitations of our study must be considered in evaluating our results. Fasting plasma glucose and triglyceride measurements were not available in our cohort, so we had to modify the definition of metabolic syndrome to use nonfasting measurements. However, because both elevated nonfasting glucose and triglyceride levels have been shown to be important risk factors for cardiovascular disease[13,26] and because measuring nonfasting rather than fasting glucose levels may even improve the ability of metabolic syndrome to predict death of cardiovascular disease,[27] it is unlikely that this would explain our results. Also, it is reassuring that metabolic syndrome per se was associated with myocardial infarction and ischemic heart disease in our cohort with risk estimates similar to those of previous studies.[10] In addition, we cannot exclude the possibility that our results might be influenced by residual confounding due to variation within each BMI category or in some of the components of metabolic syndrome. Also, recruitment of participants from the general population could lead to selection bias due to possible overrepresentation of relatively healthy overweight and obese individuals, but this would tend

Figure 3. Risk of Myocardial Infarction and Ischemic Heart Disease According to Combinations of Body Mass Index (BMI) Category (Normal Weight, Overweight, Obese) and Absence or Presence of Metabolic Syndrome

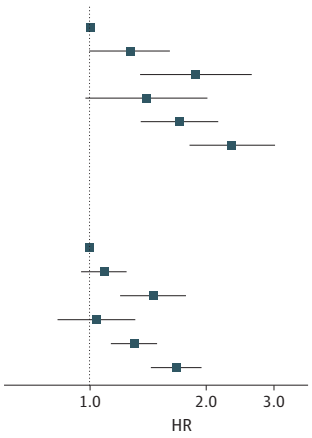
A

Myocardial Infarction

BMI Category	Metabolic Syndrome	Participants, No.	MI, No.	HR (95% CI)
Normal weight	No	28431	138	1.0
Overweight	No	17406	135	1.26 (1.00-1.61)
Obese	No	4416	46	1.88 (1.34-2.63)
Normal weight	Yes	3021	36	1.39 (0.96-2.02)
Overweight	Yes	11173	164	1.70 (1.35-2.15)
Obese	Yes	7080	115	2.33 (1.81-3.00)

Ischemic Heart Disease

BMI Category	Metabolic Syndrome	Participants, No.	IHD, No.	HR (95% CI)
Normal weight	No	28431	484	1.0
Overweight	No	17406	391	1.08 (0.95-1.24)
Obese	No	4416	129	1.45 (1.20-1.77)
Normal weight	Yes	3021	87	1.03 (0.82-1.30)
Overweight	Yes	11173	400	1.30 (1.13-1.49)
Obese	Yes	7080	290	1.67 (1.44-1.93)



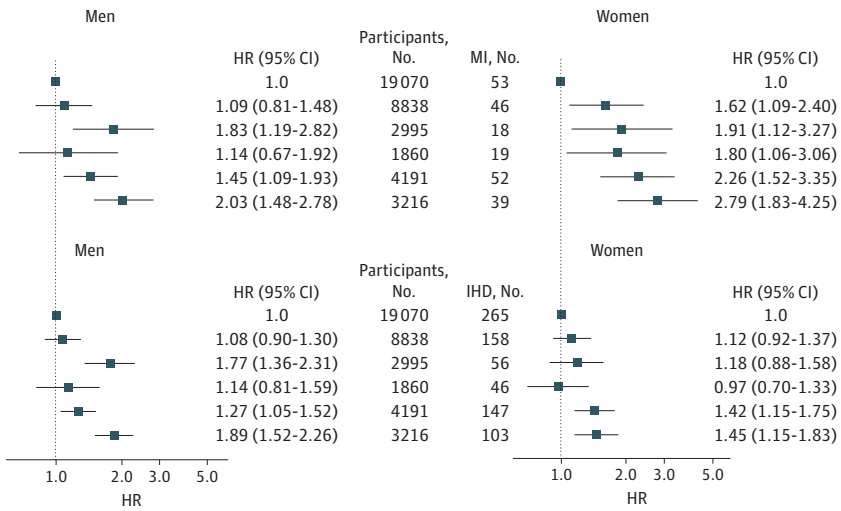
B

Myocardial Infarction

BMI Category	Metabolic Syndrome	Men: Participants, No.	Men: MI, No.	Men: HR (95% CI)	Women: Participants, No.	Women: MI, No.	Women: HR (95% CI)
Normal weight	No	9361	85	1.0	19070	53	1.0
Overweight	No	8568	89	1.09 (0.81-1.48)	8838	46	1.62 (1.09-2.40)
Obese	No	1421	28	1.83 (1.19-2.82)	2995	18	1.91 (1.12-3.27)
Normal weight	Yes	1161	17	1.14 (0.67-1.92)	1860	19	1.80 (1.06-3.06)
Overweight	Yes	6982	112	1.45 (1.09-1.93)	4191	52	2.26 (1.52-3.35)
Obese	Yes	3864	76	2.03 (1.48-2.78)	3216	39	2.79 (1.83-4.25)

Ischemic Heart Disease

BMI Category	Metabolic Syndrome	Men: Participants, No.	Men: IHD, No.	Men: HR (95% CI)	Women: Participants, No.	Women: IHD, No.	Women: HR (95% CI)
Normal weight	No	9361	219	1.0	19070	265	1.0
Overweight	No	8568	233	1.08 (0.90-1.30)	8838	158	1.12 (0.92-1.37)
Obese	No	1421	73	1.77 (1.36-2.31)	2995	56	1.18 (0.88-1.58)
Normal weight	Yes	1161	41	1.14 (0.81-1.59)	1860	46	0.97 (0.70-1.33)
Overweight	Yes	6982	253	1.27 (1.05-1.52)	4191	147	1.42 (1.15-1.75)
Obese	Yes	3864	187	1.89 (1.52-2.26)	3216	103	1.45 (1.15-1.83)



A, All participants; B, stratified by sex. Based on 71 527 individuals from the Copenhagen General Population Study without prior diagnoses of ischemic heart disease. Hazard ratios were adjusted for age, sex, smoking, plasma low-density lipoprotein cholesterol level, lipid-lowering medication use (statins for approximately 97% of participants receiving such medication), aspirin use, and physical inactivity. Body mass index was calculated as weight in kilograms divided by height in meters squared. Error bars indicate 95% confidence interval. HR indicates hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction.

to draw the results in a direction toward the null hypothesis and therefore likely cannot explain our findings. Furthermore, we studied whites only and our results may not necessarily apply to individuals of other races; however, we are not aware of data to suggest that our results should not apply to people of all races and countries. Another limitation is that we did not have information on type or dose of lipid-lowering therapy. Thus, the applied correction of nonfasting triglyceride levels corresponding to the mean reduction in individuals using simvastatin, 40 mg/d, may tend to underestimate the potential effect of other lipid-lowering agents. However, because almost all participants who were prescribed lipid-lowering medication were using simvastatin, it is unlikely that this lack of information influenced our results to a great extent. Finally, the attenuated results for ischemic heart disease compared with myocardial infarction may be due to misclassification, because the diagnostic criteria for ischemic heart disease include subjective symptoms of angina pectoris and are accordingly more prone to misclassification.

Early identification and treatment of metabolic syndrome is often perceived as presenting a major challenge for health care professionals facing the epidemic of overweight and obesity. However, the present data suggest that, even in the absence of metabolic syndrome, priority should be given to reducing rates of overweight and obesity to reduce these individuals' risk of ischemic heart disease and myocardial infarction. Also, because abdominal adiposity seems to precede the development of the other abnormalities in the

syndrome,[19] overweight and obesity may in some individuals be an early warning sign for future metabolic disturbances. Thus, weight loss and long-term maintenance of that weight loss should be encouraged in all overweight and obese individuals, regardless of presence or absence of metabolic syndrome, to reduce risk of obesity-related myocardial infarction and ischemic heart disease.

In conclusion, overweight and obesity with and without metabolic syndrome are associated with increased risk of myocardial infarction and ischemic heart disease in the general population. These findings suggest that overweight and obesity even in the absence of metabolic syndrome are not benign conditions and that weight loss should be encouraged regardless of the presence or absence of metabolic syndrome to reduce risk of myocardial infarction and ischemic heart disease. Our findings also suggest that metabolic syndrome is no more valuable than BMI in identifying individuals at risk of myocardial infarction and ischemic heart disease.

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